originally estimated to be required. Despite this magnificent accomplishment, vaccination certificates for international travel will be required by many countries for at least two additional years or until formal certification of all countries as smallpox-free has been completed by an international commission.

PAUL F. WEHRLE, MD

REFERENCES

Wehrle PF, Posch J, Richter KH, et al: Airborne smallpox in a German hospital. Bull World Health Organization 43:669-679, 1970

Bica AN, Gispen R, Grant FD, et al: WHO Expert Committee on Smallpox Eradication, Second Report. World Health Organization Technical Report Series 493, Geneva, 1972

New Drugs in the Therapy of Asthma

WITH AN increasing understanding of the molecular basis of the action of many of the more effective agents, the pharmacotherapy of asthma has reached a more rational and specific basis than in the past. In particular, the appreciation of the role of cyclic 3,5 adenosine monophosphate (CAMP), the intracellular hormone which has been shown to cause bronchial relaxation as well as inhibition of chemical mediator release (histamine and slow-reacting substance of anaphylaxis [SRS-A]), has focused new attention on the pharmacologic management of asthma.

Studies have shown that the pharmacologic activities of adrenergic agents are related to their catecholamine structure. It has been shown that the beta-adrenergic stimulant acts as a first messenger, activating the beta-receptor, adenyl cyclase complex. This catalyzes the production of CAMP from adenosine triphosphate (ATP). Theophylline, on the other hand, inhibits phosphodiesterase thus preventing the degradation of CAMP, resulting in an increase in intracellular CAMP levels.

Due to the many shortcomings of the two principal adrenergic agonists (epinephrine and isoproterenol) available for the treatment of asthma, newer beta-adrenergic agonists are in the process of being investigated while some are now available for use. These agents have three major advantages over epinephrine and isoproterenol. They are effective when given orally, have a longer duration of action and seem to be more selective as pure $beta_2$ stimulators, therefore reducing undesirable cardiovascular stimulation. The three compounds which have enjoyed the most widespread attention are metaproterenol—known in Britain as orciprenaline—(Alupent® or Metaprel®), terbutaline (Bricanyl®, Brethine®) and salbutamol (Albuterol®). Metaproternol is now available in both oral and inhalable forms. It appears to be more effective than ephedrine, but still is not completely free of cardiovascular or stimulating side effects. Terbutaline, initially available in only an injectable form, is now also available in an oral form and appears to be more potent than its predecessor, metaproterenol. Salbutomol, although it has been used in Great Britain, is still not approved for use in this country. Results of investigative studies indicate this agent may prove to be the most effective of the three beta-adrenergic agonists discussed. Salbutomol has been a more potent bronchodilator than either metaproterenol or terbutaline in both oral and aerosolized routes. Two other beta-adrenergic bronchodilators being investigated include Berotec® and Salmefamol®.

The use of the prostaglandins PGE_1 and PGE_2 as bronchial relaxants is currently being studied. However, the disadvantages of their short duration of action, upper airway irritation and induction of bronchoconstriction poses yet unsolved problems.

There is some suggestion that alpha-adrenergic blockers such as phentolamine, thymoxamine or dibenamine may have some usefulness in the treatment of asthma. With a demonstration that stimulation of the subepithelial irritant receptors of the tracheobronchial tree initiates a vagal reflex with resultant bronchospasm, there has also been renewed interest in the use of atropine by inhalation and intravenous administration, as a cholinergic inhibitor.

Because of the well known undesirable side effects of systemic corticosteroid therapy, particularly growth suppression, investigation of topically-active agents has received great emphasis. Beclomethasone diproprionate has been extensively studied in the United Kingdom and is undergoing similar trials in this country. Neither growth suppression nor suppression of the hypothalamic-pituitary-adrenal axis seems to occur. One important problem has been the appearance of oral, faucial and laryngeal infection with Monilia. This, however, seems to be more of a problem with adults rather than children. The indications for aerosol steroids probably would be: (1) children, in whom asthma is uncontrolled with cromolyn and other bronchodilators without resorting to steroids; (2) children presently steroid-dependent. The most common dose of

beclomethasone has been 100 micrograms (μg) (two puffs) three or four times daily. Cromolyn sodium prophylaxis has been widely discussed in many publications. It is important that indications for its use, the method of administration and that it should be used only as a prophylactic agent be clear to both physician and patient. It probably should be reemphasized that the drug has no use in the treatment of wheezing episodes. Finally, it should probably also be mentioned that the methyl xanthines have enjoyed a resurgence as a new appreciation of bioavailability and appropriate dosage becomes more widely known. The most widely accepted oral program for the use of theophylline is now 6 to 10 mg per kg of body weight per dose, given every six hours around the clock.

MARSHALL G. GOLDBERG, MD

REFERENCES

Siegel SC, Bernstein IL, Katz R, et al: Double-blind controlled evaluation of oral salbutamol (Albuterol). J Allergy Clin Immunol 53:83, Feb 1974

Godfrey S: The place of a new aerosol steroid, beclomethasone dipropionate, in the management of childhood asthma. Pediatr Clin North Am 22:147, Feb 1975

Piafsky KM, Oglivie RI: Drug therapy. Dosage of theophylline in bronchial asthma. N Engl J Med 292:1218, Jun 1975

Reye's Syndrome (Encephalopathy and Fatty Visceral Infiltration)

THIS CLINICOPATHOLOGICAL ENTITY, described by Reye and co-workers in 1963, is now recognized as a common, deadly illness of infants and children. The syndrome consists of a mild prodromal illness, associated with anorexia, and symptoms of an upper respiratory infection. The sudden onset of vomiting is the major sign that a serious disease may be involved, since lethargy, irrational behavior, stupor, convulsions and coma generally follow vomiting within the next 24 hours. On physical examination hyperreflexia is seen, and hypertoxicity is found in a child who may be responsive to voice commands (Stage II coma), unresponsive to all but deep pain stimuli (Stage III) or requires mechanical support for failing respiratory function, variable or weak pulses and hypotension (Stage IV). Generally, most children in Stage IV coma do not recover, whereas persistence of Stage III coma without further deterioration for at least 24 hours is a good prognostic sign.

All children with suspected Reye's syndrome should receive a lumbar puncture (normal results) to rule out infectious causes, and tests for serum glutamic-oxaloacetic transaminase, prothrombin time and blood ammonia. These three measurements of liver function are nearly always abnormal in Reye's syndrome, whereas there is no jaundice or significant hyperbilirubinemia, helping to distinguish this condition from fulminating hepatitis. Hypoglycemia is also present in approximately 50 percent of cases. A percutaneous liver biopsy specimen stained for fat is extremely helpful in establishing the diagnosis.

Treatment is nonspecific, and results difficult to evaluate. Since controlled studies of various regimens are unavailable, individual experience must be a guide to therapy. I believe that supportive treatment (electrolyte and fluid balance, reversal of metabolic acidosis and administration of glucose) is all that is necessary in patients who are in Stage III coma or better. Approximately 80 percent will begin the recovery process within 1 to 2 days after onset of coma. The real problem is a child slipping into Stage IV coma. In such circumstances, exchange blood transfusion is indicated, since 80 percent of such patients will die. It is also helpful to note the *trend* of blood ammonia in Stage III. When ammonia levels are on the rise, deterioration will probably become apparent soon thereafter. Therefore, exchange blood transfusions, perhaps combined with peritoneal dialysis, may be indicated in Stage III coma with rising blood ammonia levels.

The cause of Reye's syndrome is unknown. An association with chicken pox and influenza B has been clearly shown, but neither virus has been directly implicated. It is possible that in a child in whom the syndrome develops in the course of these illnesses an undetected error in ammonia metabolism may exist. Recent studies of hepatic urea cycle enzymes in Reye's syndrome are consistent with this possibility.

M. MICHAEL THALER, MD

REFERENCES

Reye RDK, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera—A disease entity in childhood. Lancet 2:749-752, Oct 12, 1963

Bradford WD, Parker JC, Jr: Reye's Syndrome—Possible causes and pathogenetic pathways. Clin Pediatr (Phila) 10:148-153, Mar 1971

Thaler MM, Hoogenraad NJ, Boswell M: Reye's syndrome due to a novel protein-tolerant variant of ornithine transcarbamylase deficiency. Lancet 2:438-440, Aug 24, 1974